

# Pulmonary vein isolation with complex fractionated atrial electrogram ablation for paroxysmal and nonparoxysmal atrial fibrillation: A meta-analysis

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**BACKGROUND:** Pulmonary vein isolation (PVI) is recognized as a potentially curative treatment for atrial fibrillation (AF). Ablation of complex fractionated atrial electrograms (CFAEs) in addition to PVI has been advocated as a means to improve procedural outcomes, but the benefit remains unclear.

**OBJECTIVE:** This study sought to synthesize the available data testing the incremental benefit of adding CFAE ablation to PVI.

**METHODS:** We performed a meta-analysis of controlled studies comparing the effect of PVI with CFAE ablation vs. PVI alone in patients with paroxysmal and nonparoxysmal AF.

**RESULTS:** Of the 481 reports identified, 8 studies met our inclusion criteria. There was a statistically significant increase in freedom from atrial tachyarrhythmia (AT) with the addition of CFAE ablation (relative risk [RR] 1.15,  $P = .03$ ). In the 5 reports of nonparoxysmal AF (3 randomized controlled trials, 1 controlled clinical trial, and 1 trial using matched historical controls), addition of CFAE ablation resulted in a statistically significant increase in freedom from AT ( $n = 112$  of 181 [62%] for PVI+CFAE vs.  $n =$

84 of 179 [47%] for PVI alone; RR 1.32,  $P = .02$ ). In trials of paroxysmal AF (3 randomized controlled trials and 1 trial using matched historical controls), addition of CFAE ablation did not result in a statistically significant increase in freedom from AT ( $n = 131$  of 166 [79%] for PVI+CFAE vs.  $n = 122$  of 164 [74%] for PVI alone; RR 1.04,  $P = .52$ ).

**CONCLUSION:** In these studies of patients with nonparoxysmal AF, addition of CFAE ablation to PVI results in greater improvement in freedom from AF. No additional benefit of this combined approach was observed in patients with paroxysmal AF.

**KEYWORDS:** Atrial fibrillation; Catheter ablation; Complex fractionated atrial electrogram; Pulmonary vein isolation

**ABBREVIATIONS:** AF = atrial fibrillation; AT = atrial tachyarrhythmia; CFAE = complex fractionated atrial electrogram; PVAI = pulmonary vein antrum isolation; PVI = pulmonary vein isolation.

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## Introduction

Atrial fibrillation (AF) affects more than 2 million Americans<sup>1</sup> and is associated with increased risk of stroke and death despite optimal medical therapy.<sup>2,3</sup> The observation that ectopic beats from the pulmonary veins play a major role in the initiation of AF<sup>4</sup> has led to the development of percutaneous isolation of

the pulmonary veins (PVI) as an accepted treatment for AF. PVI has resulted in high single procedural success rates for patients with paroxysmal AF,<sup>5–8</sup> but success rates for PVI alone in patients with nonparoxysmal AF are often lower, and additional ablation has been advocated by some to increase procedural success rates in this population.

This work was conducted with support from Harvard Catalyst, The Harvard Clinical and Translational Science Center (National Institutes of Health Award UL1 RR 025758 and financial contributions from Harvard University and its affiliated academic health care centers). The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic health care centers, the National Center for Research Resources, or the National Institutes of Health. Dr. Mela is a consultant to Biotronik and has lectured for Medtronic, St. Jude Medical, and Biotronik. Dr. Heist is a consultant to St. Jude Medical; has received research support from Boston Scientific and St. Jude Medical; and has lectured for Biotronik, Boston Scientific, Medtronic, St. Jude Medical, and Sorin. Dr. Verma is a consultant to Biosense Webster, Medtronic, Sanofi Aventis, Astra

Zeneca, and Servier; has lectured for Biosense Webster, Medtronic, and St. Jude Medical; and has received research grants from Biosense Webster, Medtronic, and St. Jude Medical. Dr. Singh is a consultant to Biotronik, Boston Scientific, Biosense Webster, CardioInsight, Medtronic, St. Jude Medical, CardioInsight, Thoratec, and the Sorin Group; has lectured for Biotronik, Boston Scientific, Medtronic, St. Jude Medical, and the Sorin Group; and has received research grants from Biotronik, Boston Scientific, Medtronic, and St. Jude Medical. **Address reprint requests and correspondence:** Dr. Jagmeet P. Singh, Cardiac Arrhythmia Service, Cardiology Division, Gray Building 109, Massachusetts General Hospital Heart Center, 55 Fruit Street, Boston, MA 02114. E-mail address: jsingh@partners.org. (Received January 23, 2011; accepted February 22, 2011.)

Table 1 - Baseline Characteristics of Patients Included in Meta-Analysis

	Verma (2010)		Di Biase (2009)		Deisenhofer (2009)		Lin (2009)		Oral (2009)		Elavi (2008)		Verma (2008)		Verma (2007)	
	PVI+CFAE	PVI Alone	PVI+CFAE	PVI Alone	PVI+CFAE	PVI Alone	PVI+CFAE	PVI Alone	PVI+CFAE	PVI Alone	PVI+CFAE	PVI Alone	PVI+CFAE	PVI Alone	PVI+CFAE	PVI Alone
Number of Patients	34	32	34	35	50	48	30	30	50	50	49	48	35	35	100	100
Age, mean +/- SD (years)	59±10	55±11	58±8	57±8	55±10	58±10	49±10	49±12	62±8	58±10	59±12	58±10	61±9	60±11	56±9	57±12
Male Gender (%)	74	75	88	83	82	69	80	87	82	82	65	69	74	77	63	63
LA Size, mean +/- SD (mm)	41±6	43±5	44±6	43±6	44±5	43±6	41±8	40±5	46±6	47±6	46±6	45±7	43±9	41±10	43±10	42±9
LVEF, mean +/- SD (%)	59±12	62±7	55±6	55±8	NA	NA	54±8	56±8	54±9	53±12	55	52	53±7	53±8	53±11	53±12
Duration of AF (years)	7.6±9.4	6.4±6.6	5.3±5.0	5.3±5.7	4±4	4±3	8.4±7.2	5.4±6.4	5±4	6±5	6.3±2.5	5.5±3.5	5.5±4.0	4.9±4.5	5.1±2.0	5.3±3.0

PVI = pulmonary vein isolation; CFAE = complex fractionated atrial electrogram ablation; SD = standard deviation; LA = left atrium; LVEF = left ventricular ejection fraction; AF = atrial fibrillation; NA = not available

Figure 1 Search flow diagram for reports included in the meta-analysis.

More recently, the targeting of specific sites within the atria that contain electrogram fractionation has been described as a technique for terminating AF.<sup>9</sup> These sites, termed complex fractionated atrial electrograms (CFAEs), are areas where electrograms are rapid and multiphasic or continuous and are thought to be important drivers for the maintenance of AF. Ablation of CFAEs has been proposed as a way to improve the success of PVI,<sup>10-18</sup> but the added benefit remains unclear. We conducted a meta-analysis to determine the effect of adding ablation of CFAEs to pulmonary vein isolation (PVI) for patients with paroxysmal and nonparoxysmal AF.

## Methods

### Search strategy

We performed an electronic literature search of MEDLINE (1950 to March 27, 2010), MEDLINE In-Process and other Non-Indexed Citations, EMBASE (all years, searched March 28, 2010), the Cochrane Database of Systematic Reviews (February 2010), and the Cochrane Central Register of Controlled Trials (first quarter 2010). Search strategies were developed with the help of a research librarian and are published as an Online Data Supplement. We also manually searched the bibliographies of the selected publications, our personal archives, and review articles published in the last 5 years on catheter ablation for AF.

### Eligibility

Randomized trials or controlled clinical trials that compared electrical isolation of the pulmonary veins to the same procedure with additional ablation of CFAEs were included. To be included, studies were required to report on the end point of freedom from atrial tachyarrhythmia (AT) or AF at least 3 months postprocedure. There were no language restrictions, and incomplete information (abstracts, brief reports) could be included as long as it met all other inclusion criteria. Ablation could be performed as a first-line therapy or after failure of antiarrhythmic drugs. Any method of isolation of the pulmonary veins (including PVI or pulmonary vein antrum isolation [PVAI]) was accepted as long as electrical isolation of the pulmonary veins was confirmed. Additional anatomical ablation lines performed after PVI were allowed as long as these were performed for both groups. CFAEs could be defined, identified, and ablated in

any manner, and this could be performed before or after PVI.

### End points

The primary end point was freedom from atrial arrhythmia off antiarrhythmic drugs. If the end point was unclear, the authors were contacted directly for clarification. Repeat procedures were not allowed (and were considered failure to reach the primary end point if they occurred). Secondary end points were procedure time, fluoroscopy time, all-cause mortality, pericardial tamponade, and thromboembolic events. For the purpose of this analysis, pericardial tamponade was defined as any pericardial effusion requiring percutaneous or surgical drainage.

### Data extraction

Data extraction was performed independently by 2 investigators, and results were recorded on a standardized data extraction form. Disagreements were resolved by consensus.

### Data analysis

Dichotomous outcomes were analyzed using the DerSimonian and Laird random effects model. We explored heterogeneity by visually inspecting the outcome plots and then calculating the  $I^2$  statistic as well as the  $\chi^2$  statistic;  $I^2 > 50\%$  indicated significant heterogeneity. Statistical significance was set at  $\alpha = 0.05$ . If significant heterogeneity was observed, we explored this by repeating the analysis while excluding studies with methodological differences from the rest. All statistical analysis was performed using Review Manager 5.0.21 (The Cochrane Collaboration, Copenhagen, Denmark).

Procedure time and fluoroscopy time, both continuous variables, were also analyzed using a random-effects model. Between-study variance was estimated using the DerSimonian and Laird method.

## Results

### Search results

Our electronic search identified 481 potentially eligible references; 8 of these met our inclusion criteria (Figure 1). Of these, 5 were randomized controlled trials,<sup>19-23</sup> 2 used matched historical controls,<sup>24,25</sup> and 1 study performed PVI and CFAE in 30 consecutive patients followed by PVI alone

Study	Study Design	Study Population	Study Detail
Verma et al (2010)	Randomized controlled trial	High-burden paroxysmal (n=43) and persistent (n=23) AF	<i>Intervention/comparator:</i> PVI with or without CFAE ablation <i>Endpoint:</i> Freedom from AF > 30 seconds, freedom from atrial arrhythmia <i>Follow-up:</i> 12 months <i>Monitoring for recurrence:</i> ECG and 48h holter at 3, 6, and 12 months; additional monitoring if symptomatic
Di Biase et al (2009)	Randomized controlled trial	Paroxysmal AF	<i>Intervention/comparator:</i> PVAI with or without CFAE ablation <i>Endpoint:</i> Freedom from atrial tachyarrhythmia <i>Follow-up:</i> 12 months <i>Monitoring for recurrence:</i> Event recorder for 5 months, 48h holter every 3 months
Deisenhofer et al (2009)	Randomized controlled trial	Paroxysmal AF	<i>Intervention/comparator:</i> PVI with or without CFAE ablation <i>Endpoint:</i> Freedom from atrial tachyarrhythmia <i>Follow-up:</i> 3 months <i>Monitoring for recurrence:</i> 7 day holter at 3 months
Lin et al (2009)	Controlled trial (30 consecutive patients ablated in each manner)	Nonparoxysmal AF	<i>Intervention/comparator:</i> PVI plus linear ablation with or without CFAE ablation <i>Endpoint:</i> Freedom from atrial arrhythmia <i>Follow-up:</i> Mean 19 months <i>Monitoring for recurrence:</i> Clinic visits with holters or event recorders if symptomatic
Oral et al (2009)	Randomized controlled trial	Persistent AF not terminated by PVAI	<i>Intervention/comparator:</i> PVAI with or without CFAE ablation <i>Endpoint:</i> Freedom from atrial arrhythmia <i>Follow-up:</i> Mean 10 months <i>Monitoring for recurrence:</i> Clinic visits with an event monitor at 6 months
Elayi et al (2008)	Randomized controlled trial	Permanent AF	<i>Intervention/comparator:</i> PVAI with or without CFAE ablation <i>Endpoint:</i> Freedom from AF or AT <i>Follow-up:</i> Mean 16 months <i>Monitoring for recurrence:</i> event recorder for the first 6 months, 48h holter every 3 months
Verma et al (2008)	Study subjects compared to matched controls	Paroxysmal (n=42) and persistent (n=28) AF	<i>Intervention/comparator:</i> PVAI with or without CFAE ablation <i>Endpoint:</i> Freedom from atrial arrhythmia <i>Follow-up:</i> Mean 13 months <i>Monitoring for recurrence:</i> ECG and 48h holter at 3, 6, and 12 months; loop recorders if symptomatic
Verma et al (2007)	Study subjects compared to matched controls	Paroxysmal (n=120) and nonparoxysmal (n=80) AF	<i>Intervention/comparator:</i> PVAI with or without adjuvant ablation of anterior LA CFAEs <i>Endpoint:</i> Freedom from AF or atypical flutter (including atrial tachycardia) <i>Follow-up:</i> 12 months <i>Monitoring for recurrence:</i> Rhythm transmitters for at least 3 months, then clinic visits and holter monitors every 3 months

**Figure 2** Individual study characteristics. LA = left atrium; RCT = randomized controlled trial.

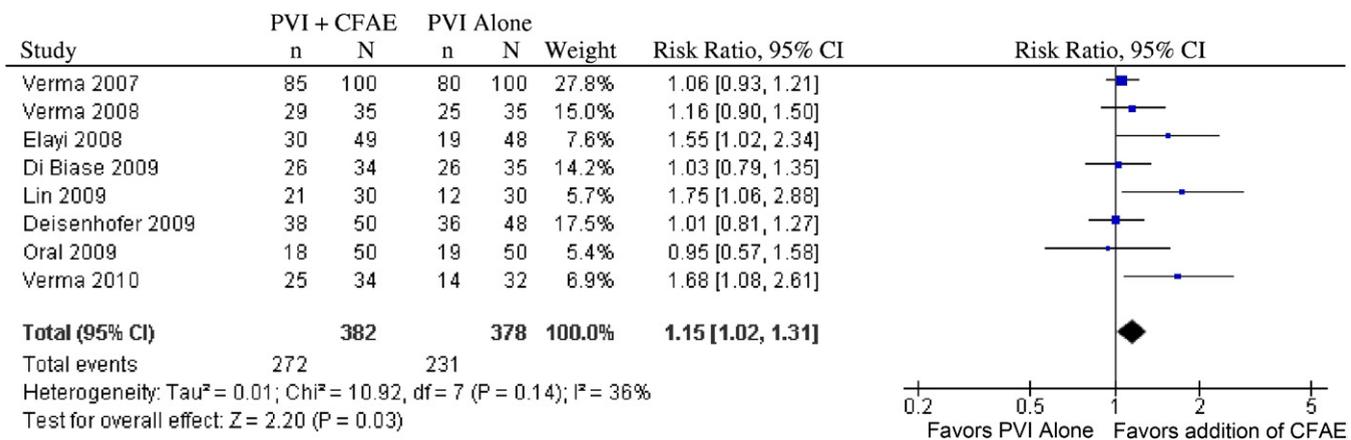


Figure 3 Freedom from atrial tachyarrhythmia for all studies. CI = confidence interval.

in 30 consecutive patients.<sup>26</sup> There were 2 studies of patients with paroxysmal AF, 3 studies of patients with nonparoxysmal AF, and 3 studies of patients with both paroxysmal and nonparoxysmal AF (Figure 2). Table 1 summarizes the baseline characteristics of the patients in the included studies. These 8 studies represent a total of 760 patients; 372 had paroxysmal AF and 388 had nonparoxysmal AF. The mean age of the patients was 57 years, and 74% were male. The mean left atrial dimension was 43 mm, and the average duration of AF was 5.6 years; 378 patients underwent PVI alone, and 382 underwent PVI+CFAE.

Of note, a single investigator (A. Verma) was the lead author on 3 of the included trials. However, the subjects in these trials did not overlap, and 2 of these trials were multicenter studies.

**Primary outcomes**

**Paroxysmal and nonparoxysmal AF studies combined**

For all studies combined, there was a statistically significant benefit to the addition of CFAE ablation to electrical isolation of the pulmonary veins in terms of freedom from AT at follow-up (relative risk [RR] 1.15, P = .03) (Figure 3). There was no evidence of heterogeneity between included studies (I<sup>2</sup> = 36%, P = .14). The meta-analysis was repeated with the 5 studies that were randomized controlled trials, and the effect size was similar, although the results were no longer statistically signifi-

cant (RR 1.17, P = .13). To further explore the results, the analysis was repeated for paroxysmal and nonparoxysmal AF individually.

**Paroxysmal AF**

Four studies (3 randomized controlled trials and 1 trial using matched historical controls) representing 330 patients reported results for patients with paroxysmal AF. One study that included patients with paroxysmal AF was not included because results were not reported for the subgroup of patients with paroxysmal AF.<sup>25</sup> The addition of CFAE ablation for patients with paroxysmal AF did not increase rates of freedom from AT (n = 131 of 166 [79%] for PVI+CFAE vs. n = 122 of 164 [74%] for PVI alone; RR 1.04, P = .52) (Figure 4). There was no heterogeneity in this study population (I<sup>2</sup> = 0%, P = .52). The analysis was repeated again using only the 3 randomized controlled trials, and the results were unchanged (RR 1.06, P = .50).

**Nonparoxysmal AF**

Five studies reported results for patients with nonparoxysmal AF. These studies represented 360 patients and included 3 randomized controlled trials, 1 controlled clinical trial, and 1 trial using matched historical controls. Addition of CFAE ablation resulted in a statistically significant increase in freedom from AT (n = 112 of 181 [62%] for PVI+CFAE vs. n = 84 of 179 [47%] for PVI alone; RR

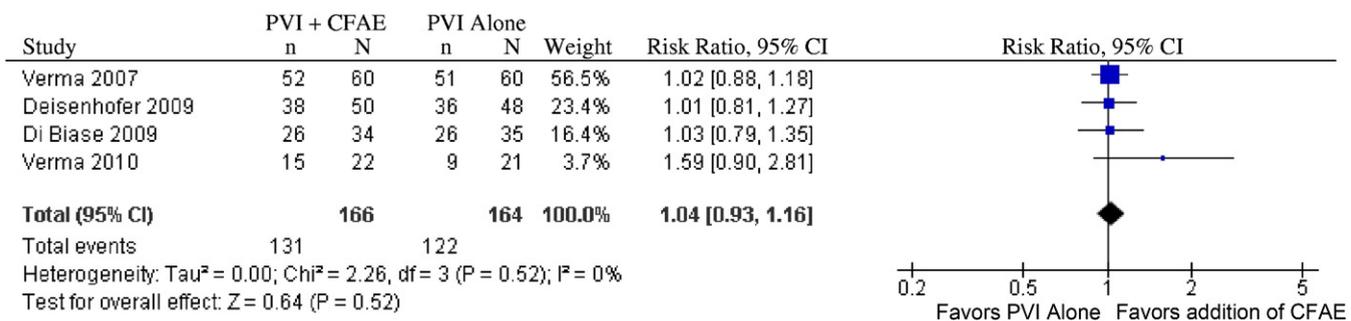
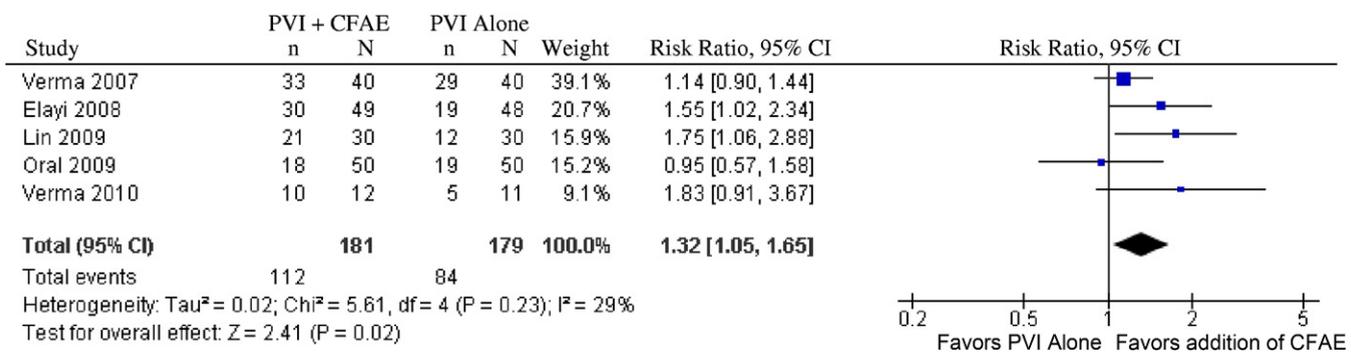


Figure 4 Freedom from atrial tachyarrhythmia for paroxysmal AF. AF = atrial fibrillation; CI = confidence interval.



**Figure 5** Freedom from atrial tachyarrhythmia for nonparoxysmal AF. AF = atrial fibrillation; CI = confidence interval.

1.32, *P* = .02) (Figure 5). There was no evidence of significant heterogeneity between included studies (*I*<sup>2</sup> = 29%, *P* = .23). The analysis was repeated using only the 3 randomized controlled trials and the effect size was similar, although no longer statistically significant (RR 1.36, *P* = .10).

**Secondary outcomes**

**Fluoroscopy time and procedure time**

Seven studies reported data for procedure time, and 7 reported on fluoroscopy time (Figure 6). The addition of CFAE ablation resulted in increased procedure time (43 ±

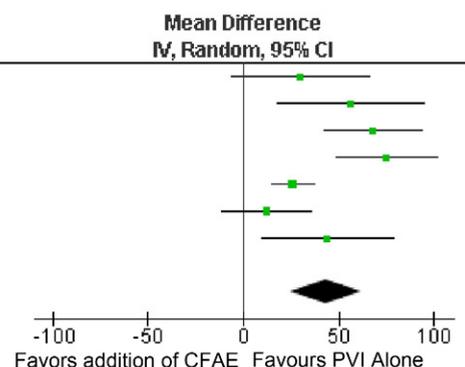
19 minutes, *P* < .001) and fluoroscopy time (14 ± 8 minutes, *P* = .001).

**Complications and mortality**

Six studies reported rates of cardiac tamponade. The rate of tamponade in the PVI alone group was 0.6% (2 of 308) and in the PVI with CFAE ablation group was 1.0% (3 of 313). This difference was not statistically significant (*P* = 1.0, Fisher exact test, 2-tailed). Thromboembolic complications were reported by 6 studies representing 592 patients. No thromboembolic complications were observed in either the PVI alone arm or the PVI with CFAE

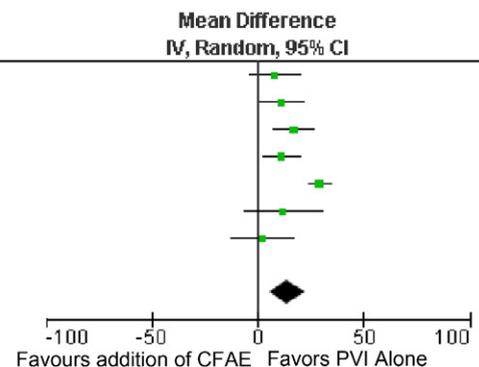
**A. Procedure Time (min)**

Study or Subgroup	PVI + CFAE			PVI Alone			Weight
	Mean	SD	Total	Mean	SD	Total	
Di Biase 2009	306	108	50	276	72	48	11.7%
Elayi 2008	239	102	49	183	91	48	11.1%
Lin 2009	181	56	30	113	45	30	15.0%
Oral 2009	329	90	50	254	47	100	14.7%
Verma 2007	188	45	100	162	37	100	19.5%
Verma 2008	251	41	35	239	58	35	15.7%
Verma 2010	225	68	34	181	74	32	12.2%
<b>Total (95% CI)</b>			<b>348</b>			<b>393</b>	<b>100.0%</b>
Heterogeneity: Tau <sup>2</sup> = 427.58; Chi <sup>2</sup> = 22.51, df = 6 (P = 0.0010); I <sup>2</sup> = 73%							
Test for overall effect: Z = 4.56 (P < 0.00001)							



**B. Fluoroscopy Time (min)**

Study or Subgroup	PVI + CFAE			PVI Alone			Weight
	Mean	SD	Total	Mean	SD	Total	
Deisenhofer 2009	71	34	50	63	25	48	13.9%
Di Biase 2009	76.8	21.8	34	65.6	22.6	35	14.8%
Elayi 2008	94	27	49	76.9	21	48	15.4%
Oral 2009	70	27	50	59	23	100	16.0%
Verma 2007	84	20	100	55	18	100	18.0%
Verma 2008	74	39	35	62	40	35	9.9%
Verma 2010	60	34	34	58	27	32	12.0%
<b>Total (95% CI)</b>			<b>352</b>			<b>398</b>	<b>100.0%</b>
Heterogeneity: Tau <sup>2</sup> = 92.35; Chi <sup>2</sup> = 28.29, df = 6 (P < 0.0001); I <sup>2</sup> = 79%							
Test for overall effect: Z = 3.26 (P = 0.001)							



**Figure 6** Procedure time (A) and fluoroscopy time (B), both in minutes.

ablation arm. No deaths were reported by any of the included studies (although not all studies reported on deaths at follow-up).

## Discussion

### Main findings

In this meta-analysis of controlled trials comparing PVI alone vs. PVI with CFAE ablation for AF, we found that the addition of CFAE ablation to PVI results in a statistically significant increase in freedom from AT at follow-up for subjects with nonparoxysmal, but not paroxysmal, AF. The added benefit of CFAE ablation comes at the cost of increased procedure time and increased fluoroscopy time. There was no statistically significant difference in the rate of tamponade, and the rate of other complications was low enough to prohibit statistical analysis. To our knowledge, this is the first meta-analysis addressing these questions.

PVI aims to electrically isolate the pulmonary veins and thus the triggers of AF. This procedure has resulted in high success rates for paroxysmal AF, but is inadequate for many patients with nonparoxysmal AF. As AF moves from the paroxysmal to the nonparoxysmal state, the atria undergo both structural and electrical remodeling, resulting in areas of fibrosis and slowed conduction. These structural changes facilitate anisotropy, and the associated pivoting and colliding of wavelets, which result in regions with fractionated electrograms. It was first proposed by Konings et al<sup>27</sup> that these areas are critical to the persistence of AF. Nademanee et al<sup>9</sup> were the first to show that substrate modification through ablation of CFAEs could be used to terminate AF. As AF moves from the paroxysmal to the persistent state, abnormal atrial substrate plays a larger role in the persistence of AF. As a result, simply isolating the pulmonary vein triggers of AF may not be sufficient to prevent recurrence of nonparoxysmal AF. In this meta-analysis, targeted substrate ablation was shown to improve procedural outcomes for patients with nonparoxysmal AF, possibly by eliminating the specific substrate responsible for perpetuation of AF in these patients.

In the pooled analysis of studies of nonparoxysmal AF, the use of CFAE ablation as an adjunct to PVI resulted in an increase in freedom from AT at follow-up (RR ratio 1.32, 95% confidence interval 1.05 to 1.65). This analysis included 5 studies, 4 of which showed improved long-term efficacy over anatomical ablation alone. Oral et al<sup>22</sup> found no improvement in outcome with the addition of CFAE ablation. This study differed from the others in the group in several ways. First, the study population had larger left atrial diameters (4.65 cm on average vs. 4.29 cm for the other studies), and the success rates of the procedures were lower. Given this, the patient population may have had more advanced AF that was less suitable for ablation in general, biasing against an effect. Finally, the investigators limited CFAE ablation to 2 hours or stopped ablating CFAEs when AF terminated.

In the pooled analysis of studies of paroxysmal AF, the use of CFAE ablation as an adjunct to PVI did not result in an increase in freedom from AT at follow-up (RR ratio 1.04, 95% confidence interval 0.93 to 1.16). One of the 4 studies, Verma et al,<sup>19</sup> showed a nonsignificant trend toward benefit from the combined approach ( $P = .14$ ). Interestingly, this study included patients with high-burden paroxysmal AF, possibly accounting for this trend.

### Study limitations

Meta-analysis was developed for application to randomized trials. However, there has been a recent trend in the use of meta-analysis for nonrandomized studies.<sup>28</sup> To address the fact that we included nonrandomized data, we performed a sensitivity analysis by repeating each part of the meta-analysis using only the data from randomized controlled trials. The effect sizes remained remarkably consistent, although the statistically significant findings were no longer significant with the smaller number of included studies.

The second limitation of this study was the variation in the technique of ablation between centers. Different studies used different methods to electrically isolate the pulmonary veins (PVI or PVAI). One study, Lin et al<sup>26</sup> performed linear ablation by an anatomic approach after PVI. In addition, the definition of CFAEs, the method of identification of CFAEs (visual identification or automated mapping), and the method of CFAE ablation differed between studies. For example, the study by Verma et al<sup>24</sup> limited CFAE ablation for the anterior left atrium and the anterior septum, whereas the study by Deisenhofer et al<sup>21</sup> performed a more extensive CFAE ablation involving both the left and right atria. Oral et al<sup>22</sup> limited CFAE ablation to 2 hours. However, the average additional procedure time for CFAE ablation was only 75 minutes, which was similar to the other included studies and comfortably below their 2-hour limit.

Another limitation of this study was the variation on the length of follow-up. Deisenhofer et al<sup>21</sup> had only 3 months of follow-up. In their study, 2 subjects who were classified as procedural successes at 3 months later developed atrial tachycardias that required ablation. These patients would have been considered treatment failures in any of the other studies that had a longer period of follow-up. The study by Lin et al<sup>26</sup> had different follow-up durations for the intervention and control groups. By chance, this did not affect the analysis because both curves reached a plateau by 15 months.

A final limitation is that Verma et al<sup>19</sup> had a small percentage of patients still on antiarrhythmic drugs at follow-up. This was allowed in this analysis for 3 reasons: the study protocol specified that patients should be taken off antiarrhythmic drugs after 2 months, a high percentage (96%) of subjects considered to have a successful postablation outcome were off antiarrhythmic drugs, and the small number of subjects still on antiarrhythmic drugs were evenly distributed between the groups.

## Conclusion

In this meta-analysis of randomized controlled trials and controlled clinical trials, addition of CFAE ablation to PVI results in greater improvement in freedom from atrial arrhythmia for patients with nonparoxysmal AF, but not for patients with paroxysmal AF. This improvement comes at the cost of longer fluoroscopy time and procedure time. This analysis provides another piece of evidence that CFAE ablation may be a useful adjunct to PVI for patients with nonparoxysmal but not paroxysmal AF. The analysis was limited by the retrospective nature of some of the studies in addition to variation in the technique of ablation between centers. More randomized trials are needed to fully evaluate the benefits of CFAE ablation.

## Acknowledgements

The authors thank Eric A. Macklin, PhD, for his assistance in creating a random-effects model to analyze procedure time and fluoroscopy time.

## Appendix

### Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.hrthm.2011.02.033](https://doi.org/10.1016/j.hrthm.2011.02.033).

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